REVIEW

Ischemic Stroke Risk With Oral Contraceptives
A Meta-analysis

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Context The relationship between ischemic stroke and oral contraceptive (OC) use has been studied for 40 years, but disagreement about an association persists.

Objective To review available literature to determine whether OC use is associated with increased stroke risk.

Data Sources Studies published from January 1960 through November 1999 were identified from electronic databases (MEDLINE, BIOSIS, and Dissertation Abstracts Online), *Index Medicus*, bibliographies of pertinent review articles and pertinent original articles, textbooks, and expert consultation.

Study Selection From 804 potentially relevant references retrieved, 73 were studies investigating risk of ischemic stroke with OC use. Two reviewers independently applied the following inclusion criteria: more than 10 stroke cases sampled, clear stroke subtype differentiation, concurrent controls included, adequate data included to determine relative risks (RRs) and confidence intervals (CIs), analysis controlled for age, and no later publication of identical data. A third investigator adjudicated disagreements. Sixteen studies met all inclusion criteria and were included in the meta-analysis.

Data Extraction Two investigators independently extracted data, with disagreements resolved through discussion.

Data Synthesis The 16 studies were analyzed using random effects modeling. Current OC use was associated with increased risk of ischemic stroke (RR, 2.75; 95% CI, 2.24-3.38). Smaller estrogen dosages were associated with lower risk ($P=.01$ for trend), but risk was significantly elevated for all dosages. Studies that did not control for smoking ($P=.01$) and those using hospital-based controls ($P<.001$) found higher RRs, but no other patient characteristics or elements of study design were important. The summary RR was 1.93 (95% CI, 1.35-2.74) for low-estrogen preparations in population-based studies that controlled for smoking and hypertension. This translates to an additional 4.1 ischemic strokes per 100 000 nonsmoking, normotensive women using low-estrogen OCs, or 1 additional ischemic stroke per year per 24 000 such women. The RR of stroke due to OC use was not different in women who smoked, had migraines, or had hypertension.

Conclusions Summary results indicate that risk of ischemic stroke is increased in current OC users, even with newer low-estrogen preparations. However, the absolute increase in stroke risk is expected to be small since incidence is very low in this population.

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ORAL CONTRACEPTIVES (OCs) are prescribed to more than 10 million US women and 78.5 million women worldwide.[1,2] Efficacy and ease of use are well established,[3] but concerns about safety have persisted since their introduction in 1960.[4,5] Some studies have suggested that OC use is associated with increased risk of stroke,[6-20] venous thrombosis,[21-25] pulmonary embolism,[9,10,26] myocardial infarction,[27-32] and, recently, cerebral venous sinus thrombosis (CVST).[33-36]

The association between ischemic stroke and OC use has been evaluated in many studies.[8-18,20,37-45] Results have been variable with some finding increased stroke risk in OC users[8-18] and a few documenting a protective effect in past users.[15,39] A randomized trial of OC use has not been feasible, so all published studies are observational. These study designs are especially susceptible to bias since inaccurately measured or unknown risk factors, such as smoking and hypertension, may be unbalanced between the groups compared.[46] Further, the treatments may vary over time and, in retrospective studies, women may recall information imperfectly.[5,47]

Since a large-scale randomized trial to evaluate OC adverse effects may never be performed, it is essential to draw conclusions from the existing studies to advise women about the most popular form of reversible birth control. We used meta-analysis as a systematic approach to review studies of the risk of ischemic stroke with OC use and to evaluate potential reasons for discrepant results.

METHODS

We reviewed the medical literature published after the introduction of OCs in 1960. We searched from January 1960 to November 1999 using *Index Medicus* (before 1966), MEDLINE (after 1966), BIOSIS (after 1985), and Dissertation Abstracts Online (North American Universities). The following key words and subject terms were searched: *oral contraceptives (side effects, complications), stroke, estrogen, cerebral, ische-*

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mia, thrombosis, and *venous sinus*. All languages and publication types were included. Any reference that might contain data evaluating stroke risk with OCs was retrieved, including review articles. Bibliographies of pertinent articles and reviews were searched for additional references. Relevant textbooks and foreign-language articles were also reviewed. An expert in the field was consulted for additional sources.

Two investigators (L.A.G., S.K.M.) independently applied inclusion criteria for articles. A third investigator (S.C.J.) adjudicated disagreements. The following inclusion criteria were used: (1) greater than 10 cases of ischemic stroke or CVST, (2) clear differentiation of ischemic and hemorrhagic stroke, (3) cohort design or case-control design with controls gathered within 2 years of cases, (4) sufficient data provided to determine the odds ratio (OR) or relative risk (RR) and confidence intervals (CIs) comparing OC users to nonusers, (5) controlled for age in study design or analysis, and (6) no later study fully reported the same data.

Two investigators (S.C.J., L.A.G.) independently abstracted data from included articles. All disagreements were resolved through discussion. Definitions of current, past, and ever use of OCs were taken directly from the included articles. Definitions of past and ever use were consistent between studies; however, current users were variably defined, with limits for last use ranging from 2 weeks to 12 months prior to the stroke. Potential confounders were considered controlled when they were used to exclude subjects, used to match controls, or included in multivariable analysis. Definitions of covariates, such as smoking, hypertension, and alcohol use, were taken directly from included studies. Estrogen dosage was abstracted directly when it was defined. Otherwise, it was classified by the dosage used by the majority of participants (n=3) or estimated from the prevailing use pattern of the region at study onset (n=8). A firm diagnosis of ischemic stroke was defined as one confirmed by computed tomography, magnetic resonance imaging, or angiography. Refusal rates were based on the percentage of eligible participants solicited who declined participation.

Rules for choosing risk estimates to include in the meta-analysis were established a priori. Risk estimates used in the primary analysis were those that controlled for the greatest number of potential confounders by stratification, matching, or multivariable analysis. When there were multiple publications from a given study, unique results were retained.[20,37,41,43,44,48] Results for stroke incidence were chosen when provided; otherwise, mortality results were included. The risk estimate for current use vs noncurrent use (past or never) was included whenever possible. When it was not provided, risk estimates for current-vs-never use or ever-vs-never use were chosen in that order. Variances were calculated from adjusted CIs when available, or raw data when CIs were not provided. To evaluate the stability of the overall risk estimate, a sensitivity analysis was performed by iteratively eliminating each study and calculating the resulting RR. Subgroup analyses to evaluate heterogeneity and bias were determined a priori. Data from a single study were not duplicated within a stratum. All studies dichotomized age using 35 or 40 years as a cut point; to simplify analysis, we chose a single cut point of 35 years, classifying estimates based on the majority age of the subgroup. A separate analysis was conducted to evaluate the association between OCs and CVST.

Summary risk estimates were calculated using a general-variance–based random effects method, weighting individual study results by the inverse of their variance.[49] Since stroke risks were small, ORs accurately estimate RRs[50]; we report all results as RRs for simplicity. Homogeneity was calculated from individual study risk estimates using a general-variance–based method.[49] Results were defined as heterogeneous when homogeneity was unlikely ($P<.10$). A 2-tailed z test was used to detect differences across dichotomous subgroups. The nonparametric trend test of Cuzick[51] was used to detect trends in risk by estrogen dosage. Multivariable least squares meta-regression was used to assess OC stroke risk controlling for a series of covariables and weighting study RR estimates by the inverse of the variance.[52] Variables not contributing to the model ($P<.10$) were eliminated in a stepwise fashion. Publication bias was evaluated by a funnel plot of sample size vs RR[49] and by the Kendall τ rank correlation method.[53] For these calculations, sample size was defined as the number of ischemic stroke cases included.

RESULTS

Of 10409 references identified, 804 were considered potentially relevant. These were identified with MEDLINE (n=489), *Index Medicus* (n=54), Dissertation Abstracts Online (n=1), BIOSIS (n=121), and bibliographic review (n=139). Seventy-three case-control or cohort studies examined OC use and risk of ischemic stroke. Fifty-one excluded studies failed to meet 1 or more of the inclusion criteria, as follows: 10 or fewer ischemic stroke cases (n=34), inadequate definition of stroke subtype (n=22), inadequate information to determine RR and CIs (n=30), failure to control for age (n=5), and redundant data reporting in a later study (n=8). Six others were follow-up reports of prior studies that contributed new data only to our subgroup analyses.[20,37,41,43,44,48] A full listing of excluded studies and reasons for exclusion can be found at the Web site http://www.ucsf.edu/brain/exclusion.htm.

Sixteen independent studies met all inclusion criteria (TABLE) and their RR estimations were included in the overall meta-analysis (FIGURE 1). A funnel plot showed a symmetrical distribution about the mean effect size (FIGURE 2), as would be expected in the absence of publication bias.[49] Kendall τ calculation also failed to demonstrate evidence of publication bias ($P=.47$).

The overall summary risk estimate for ischemic stroke in current OC users compared with those not currently using OCs was 2.75 (95% CI, 2.24-3.38, $P<.001$). Eleven of 16 studies

found statistically significant positive summary RRs, while 5 studies showed RRs that were elevated, but not significant. Independent RR estimates ranged from 1.18 to 8.80. A plot of RR vs year of study onset showed decreasing RR with time (P=.006 by weighted log linear regression) (FIGURE 3). There was heterogeneity among the studies in the overall RR estimate ($P=.01$), suggesting that differences in study results were not due to chance alone. In a sensitivity analysis iteratively eliminating each study from the overall analysis, the summary RR ranged from 2.63 to 3.00 and the lower limit of the 95% CI never crossed 1 (2.11-2.45).

To examine whether differences in study design accounted for heterogeneity in results, we stratified studies by design features. Relative risk estimates remained significantly elevated in all strata (FIGURE 4). Stratifying study results by control of potential confounders, there was no evidence of heterogeneity only in those studies controlling for alcohol use ($P=.12$) and those failing to control for smoking ($P=.12$), hypertension ($P=.10$), or both smoking and hypertension ($P=.21$). Studies controlling for smoking ($P=.01$) and controlling for both smoking and hypertension ($P=.04$) yielded smaller RR estimates than studies not controlling for these factors.

Smaller estrogen dosages were associated with a less elevated risk of stroke ($P=.01$), and evidence of heterogeneity was reduced after stratification by dose (Figure 4). Newer-generation preparations of progesterone tended to be associated with less elevated risk, based on the 3 studies with consistent classification schemes.[8,15,23,44] Within generations of progesterone, there was a nonsignificant trend for increasing estrogen dose to be associated with higher stroke risk (first generation: <50 µg RR, 2.19 [95% CI, 1.13-4.27], ≥50 µg RR, 3.95 [95% CI, 2.42-6.45]; second generation: <50 µg RR, 2.90 [95% CI, 2.24-3.76], ≥50 µg RR, 3.63 [95% CI, 2.30-5.74]; third generation: <50 µg RR, 2.25 [95% CI, 0.82-6.15], ≥50 µg, no data), while no differences were seen between progesterone generations at equivalent estrogen dosages.

Summary RR estimates for cohort studies tended to be greater than for case-control studies (Figure 4). Studies with hospital controls found significantly greater RR estimates than those with population controls ($P<.001$). The RR for population-based studies of low-estrogen preparations controlling for both smoking and hypertension was 1.93 (95% CI, 1.35-2.74), but results were still heterogeneous. Stroke risk was associated with current OC use but not with past use.

The relative stroke risk with OC use was minimally affected by the presence of other risk factors (Figure 4). Similar RRs were found for smokers and nonsmokers and in patients with and without a history of migraine. History of hypertension and age older than 35 years also were not associated with a greater RR with OC use.

Table. Characteristics of Studies Examining Oral Contraceptive (OC) Use and Ischemic Stroke Risk*

Cohort Study, y	Region	Years of Study	Current/Noncurrent OC Users, Person-Years	Estrogen Dose, µg	Losses to Follow-up, % per Year	Firm Diagnoses
Mant et al,[12] 1998	England, Scotland	1968-1994	74 169/123 655‡	50	0.4	ND
RCGP,[20] 1983†	United Kingdom	1968-1979	165 909/600 000	>50	6.4	ND
Ramcharan et al,[45] 1981	United States	1968-1977	5660/100 437	>50	1.4	ND

Case-Control Study, y	Region	Years of Study	Control Type	No. of Cases/ Controls	Estrogen Dose, µg	Cases/Controls Refusal Rate, %	Firm Diagnoses
Vessey and Doll,[9] 1969	England	1964-1967	H	19/168	>50	7.0/5.2	21
Sartwell et al,[10] 1969	United States	1965-1968	H	19/19	>50	27.6/ND	ND
Hannaford et al,[16] 1994†	United Kingdom	1968-1990	P	45/135	50	2.9/ND	ND
CGSS,[18,37] 1973, 1975	United States	1969-1971	H, P	140/450	>50	9.7/15.6	ND
Mettinger et al,[11] 1984	Sweden	1973-1977	P	118/429	50	10/ND	75
Carolei et al,[42,43] 1996, 1993	Italy	1984-1988	H, P	78/156	≥50	ND/2.5	100
Lidegaard,[14] 1993	Denmark	1985-1989	P	295/1147	50, <50	16.9/13.5	90
Haapaniemi et al,[17] 1997	Finland	1985-1990	H	140/126	≤50	0/0	91
Thorogood et al,[38] 1992	England	1986-1988	O	21/38‡	<50	ND/ND	ND
WHO Collaborative,[5,44,48] 1996, 1999, 1999	Worldwide	1989-1993	H	697/1962	≥50, <50	ND	99
Petitti et al,[39,41] 1996, 1998	United States	1991-1994	P	144/774	<50	9.6/ND	99
Schwartz et al,[40,41] 1997, 1998	United States	1991-1995	P	60/485	<50	15/27	92
Heinemann et al,[15] 1998	Europe	1993-1996	H, P	220/775	≥50, <50	ND	98
Lidegaard et al,[13,23] 1999, 1998	Denmark	1994-1995	P	219/1041	50, <50	12.3/10.5	ND

*HTN indicates hypertension; SES, socioeconomic status; ND, no data; RCGP, Royal College of General Practitioners; H, hospital controls; P, population controls; CGSS, Collaborative Group for the Study of Stroke in Young Women; O, outpatient controls; and WHO, World Health Organization.
†The earlier RCGP cohort study data are used for subgroup analysis of cohort studies, but do not contribute to the overall summary relative risk calculation.
‡Mant et al,[12] current/never OC users; Thorogood et al,[38] ever/never OC users; all other studies, current/noncurrent OC users.
§Racially homogeneous population.
‖SES controlled for (+) in European subset, not controlled for (–) in developing countries subset.

In meta-regression analysis, estrogen dosage, control of smoking, and firm diagnosis of ischemic stroke were the only study variables contributing to RR estimates. The summary adjusted RR estimate was 1.65 (95% CI, 1.49-1.82, $P<.001$) for current, low-estrogen OC use in studies controlling for smoking.

Only 2 studies evaluating risk of CVST with OC use were identified.[33,34] The summary RR for CVST in current users was 15.9 (95% CI, 6.98-36.2).

COMMENT

Adverse effects of OC use have been a major concern since their introduction 40 years ago.[4,5] Many large studies of OC use and stroke risk have been performed, but disagreement about the association remains. In our systematic review of the literature, all 16 studies meeting inclusion criteria showed a positive association between current OC use and ischemic stroke risk, and the association reached significance in 11 studies. The overall summary risk estimate for ischemic stroke among current OC users was 2.75 (95% CI, 2.24-3.38). It remained elevated for low-estrogen preparations in population-based studies controlling for smoking and hypertension (RR, 1.93; 95% CI, 1.35-2.74). Thus, this meta-analysis suggests that current OC use is a risk factor for ischemic stroke.

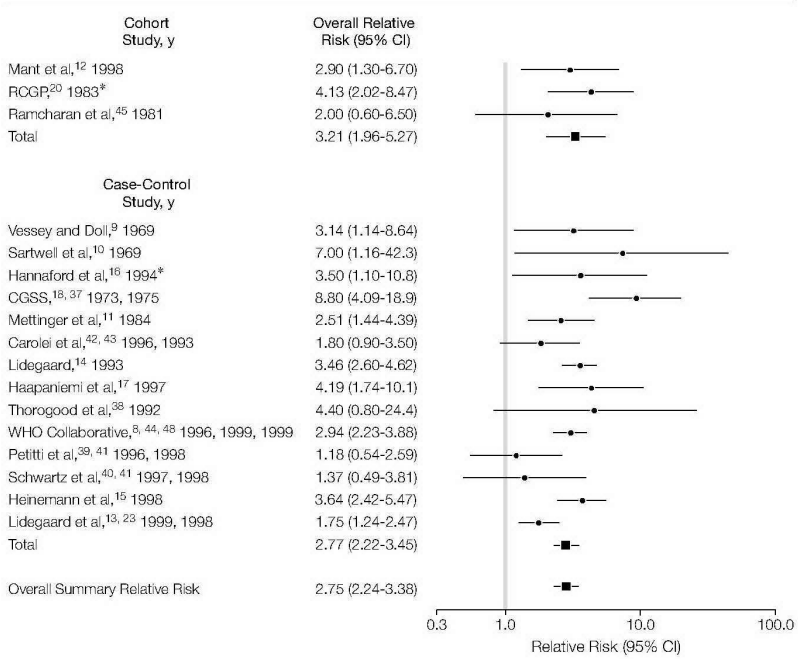
A meta-analysis depends on the quality of the included studies.[49,54] Since a randomized trial of OC use has never been performed, all studies are observational. As such, they are particularly susceptible to bias when other risk factors are unbalanced between OC users and nonusers.[5,47,55] Further, differences in risk estimates between the individual studies were larger than would be expected by chance alone, with studies in the overall estimate failing a test of homogeneity. While the random-effects model of meta-analysis attempts to encompass nonrandom variation between study results by broadening the CI of the RR estimates,[49] the source of these differences must be examined to understand the role of design in study outcomes.[56] We performed a number of subgroup analyses to evaluate which study design elements contributed to this heterogeneity.

Cohort studies tend to be less susceptible to bias than case-control studies because, in the cohort design, characteristics of cases and controls do not influence inclusion into the study differentially.[50] Both case-control and cohort studies showed similar positive associations between OC use and ischemic stroke (Figure 4), suggesting that this aspect of study design was unimportant. Population-based studies found significantly lower risk estimates, suggesting that OC use is underestimated in hospital-based con-

Controlled for				
Race	HTN	Smoking	Alcohol	SES
+	+	+	–	+
–	–	+	–	+
–	–	+	–	+

Controlled for				
Race	HTN	Smoking	Alcohol	SES
–	–	–	–	–
+	+	–	–	+
+	–	+	–	+
+	–	–	–	+
–	–	–	–	–
+§	+	+	+	–
+§	+	+	–	+
+§	+	+	+	–
–	+	–	–	–
–	+	+	–	+/–‖
+	+	+	–	+
+	+	+	+	+
–	+	+	+	–
+§	+	+	–	+

Figure 1. Overall Relative Risk for Ischemic Stroke and 95% Confidence Intervals (CIs) for Included Studies



RCGP indicates Royal College of General Practitioners; CGSS, Collaborative Group for the Study of Stroke in Young Women; and WHO, World Health Organization. The asterisk indicates that the earlier RCGP cohort study data are used for subgroup analysis of cohort studies, but do not contribute to the overall summary relative risk calculation.

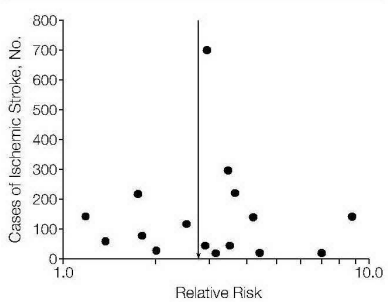
trols resulting in biased RRs. Inadequate control of other stroke risk factors could also bias study results. When data were stratified by whether specific risk factors were controlled in the design or analysis (Figure 4), we found that studies failing to control for smoking tended to find larger RRs ($P=.01$). These studies were generally performed in the 1960s and 1970s when smoking and OC use were positively correlated.[57] Inadequate control of smoking would tend to attribute to OCs the elevated stroke risk from smoking, accounting for the larger RR estimates.

The elevated risk of ischemic stroke was less with lower estrogen dosages, falling from an RR of 4.53 with more than 50 µg to an RR of 2.08 with less than 50 µg. Population-based studies using low-estrogen preparations and controlling for both smoking and hypertension found lower risks (RR, 1.93; 95% CI, 1.35-2.74). While meta-regression found an RR of 1.65 for the low-estrogen dosage in studies controlling for smoking, this estimate can only be interpreted as corroborative due to the limitations of meta-regression,[58] including instability of summary estimates with few included studies.

Analysis of progesterone type suggested nonsignificant decreasing risk with the newer formulations, with an RR of 3.21 (95% CI, 2.16-4.77) in first-generation preparations and an RR of 2.11 (95% CI, 0.96-4.64) in third-generation preparations. In stratified analysis, there was a suggestion that lower estrogen dosages in later-generation estrogen preparations may account for the difference.

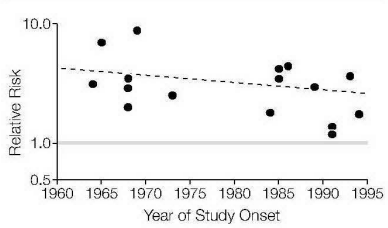
Given the heterogeneity of study results incorporated into the summary risk

Figure 2. Funnel Plot of Study Relative Risk Estimates vs Number of Cases of Ischemic Stroke



An asymmetrical distribution of points about the overall summary relative risk (arrow) is considered evidence of publication bias, absent here.

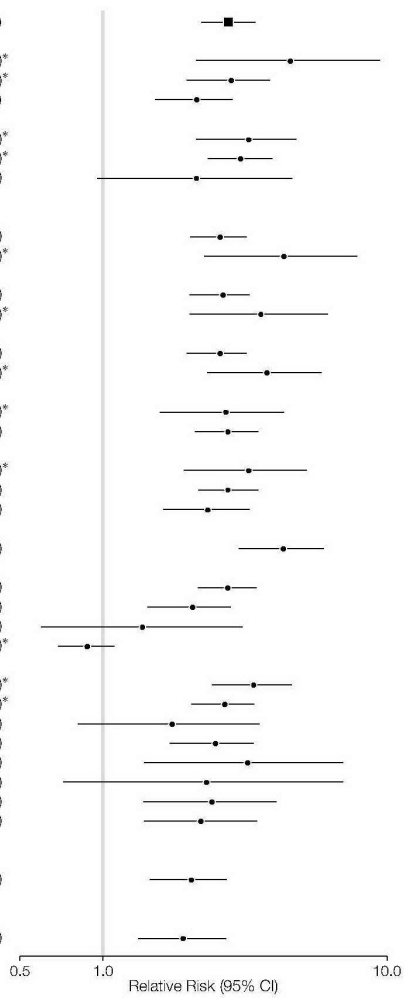
Figure 3. Year of Study Onset vs Relative Risk Estimate for Each Included Study



A log linear model was fitted to the data weighting each study by the inverse of its variance (dashed line).

Figure 4. Influence of Study Characteristics on Estimation of Relative Risk (and 95% Confidence Intervals [CIs]) of Oral Contraceptives (OCs) for Ischemic Stroke

Data Stratifications	No. of Studies	Relative Risk (95% CI)
Overall	16	2.75 (2.24-3.38)
Estrogen dose		
High (>50 µg)	4	4.53 (2.17-9.50)*
Medium (50 µg)	5	2.78 (2.00-3.85)*
Low (<50 µg)	7	2.08 (1.55-2.80)
Progesterone type†		
First generation	3	3.21 (2.16-4.77)*
Second generation	3	3.05 (2.37-3.91)*
Third generation	3	2.11 (0.96-4.64)
Control for risk factors in study design		
Smoking		
Yes	11	2.55 (2.07-3.14)
No	5	4.27 (2.34-7.82)*
Hypertension		
Yes	11	2.58 (2.08-3.22)
No	5	3.56 (2.05-6.18)*
Smoking and hypertension		
Yes	9	2.52 (2.01-3.16)
No	7	3.75 (2.39-5.91)*
Alcohol use		
Yes	4	2.66 (1.63-4.33)*
No	12	2.77 (2.18-3.51)
Study design type		
Cohort	3	3.21 (1.96-5.27)*
Case-control	14	2.77 (2.22-3.45)
Population controls	9	2.34 (1.67-3.27)
Hospital controls (includes outpatient controls)	8	4.32 (3.11-6.02)
Exposure classification		
Current vs noncurrent use	14	2.77 (2.22-3.44)
Current vs never use	7	2.03 (1.47-2.82)
Ever vs never use	3	1.37 (0.60-3.11)
Past vs never use	9	0.86 (0.69-1.08)*
Independent effect of OC use among:		
Smokers	7	3.41 (2.51-4.63)*
Nonsmokers	7	2.68 (2.09-3.43)*
With history of hypertension	3	1.73 (0.83-3.60)
Without history of hypertension	5	2.47 (1.80-3.38)
With migraine history	4	3.22 (1.45-7.16)
Without migraine history	4	2.30 (0.74-7.18)
Age <35 y	7	2.41 (1.42-4.09)
Age ≥35 y	7	2.23 (1.42-3.50)
Low-dose OCs (<50 µg)		
Study design control for smoking and hypertension	6	2.04 (1.51-2.76)
Population-based studies controlling for smoking and hypertension	5	1.93 (1.35-2.74)



Asterisk indicates that there was no evidence of heterogeneity in the study results. Dagger indicates that progesterone generation represents classification of progesterone type as defined by individual study authors.

estimates, the magnitude of the estimates must be interpreted with caution.[55,59] However, all 5 studies that evaluated low-estrogen preparations and controlled for smoking and hypertension showed a positive association of OC use with stroke risk, and 3 of these reached significance. Overall, these results suggest that while ischemic stroke risk has decreased with newer, low-estrogen preparations, a significant risk persists with the OC preparations used today.

Two recent, rigorous studies of low-estrogen OCs in the United States found insignificantly elevated RRs that were smaller than the summary RR for similar preparations in this meta-analysis.[39-41] Whether the disparity is due to more complete control of confounding factors in these 2 studies, selection of low-risk individuals for OC treatment with overcorrection for confounders, or chance cannot be answered from this analysis.

Some studies found greater stroke risk among OC users with additional risk factors, such as hypertension,[37] smoking,[8,12,15,37] and migraine.[37,41,48] Assuming that OC use and other risk factors act synergistically to elevate stroke risk, it has been suggested that OC use in women with these risk factors is riskier than for those without them. This has led to recommendations to avoid OC prescriptions for smokers and those with hypertension.[4,5,8,41] We analyzed separately results from studies examining the effect of OC use among those with other risk factors. Oral contraceptive use appeared to impart a similar ischemic stroke risk among smokers and nonsmokers. Further, there were no differences in OC RR among those with and without hypertension, with and without migraine, and younger and older than 35 years. This suggests that the ischemic stroke risk of OC use is independent of smoking, hypertension, migraine history, and age. However, current prescribing practices may have resulted in unbalanced levels of additional risk factors, such as fewer pack-years in OC users who smoke, and inadequate control of level of smoking could obscure an interaction between smoking and OC use. Also, since these risk factors increase baseline risk of stroke, a greater absolute increase in stroke risk with OC use would be anticipated. Further, whether other adverse effects of OC use, such as deep venous thrombosis, are also independent of additional risk factors is unknown. Therefore, it may still be appropriate to avoid OC prescriptions for smokers and those with hypertension.

Cerebral venous sinus thrombosis is a rare,[34] potentially underdiagnosed cause of ischemic and hemorrhagic strokes.[60] Two recent studies suggested that OC use elevates risk of CVST.[33,34] We found a markedly elevated summary risk estimate of 15.9 (95% CI, 6.98-36.2) for CVST in current OC users. Additional analysis of these 2 studies examining third-generation preparations alone found very different effects, with RRs of 2 and 32.9.[35,36] If high risk of CVST with OC use is confirmed, undiagnosed CVST may account for a significant portion of ischemic strokes attributed to OCs. Further studies are needed to clarify the relationship between CVST and OC use.

More than 10 million women use OCs in the United States.[1] With an RR of 1.93 due to low-estrogen OCs, a woman's annual stroke risk would be expected to increase from 4.4 to 8.5 per 100 000 based on background incidence rates.[61] Therefore, treatment of 24 000 women would be expected to lead to a single additional ischemic stroke each year.[62] Approximately 425 total ischemic strokes per year would be attributable to OC use in the United States. Although we found no significant difference in stroke risk between smokers and nonsmokers, given the elevated risk of stroke in smokers,[63] we estimated smokers to have an absolute annual risk increase of 6.9 per 100 000 with low-estrogen OCs, equivalent to 1 additional ischemic stroke a year for every 15 000 smokers taking OCs.

If OC use were replaced by the second most popular birth control method, the male condom,[1] an estimated 687 000 additional unintended pregnancies would result per year in the United States,[3] with an associated 26 strokes and 33 deaths based on complication rates of pregnancy and abortion.[64-67] Although the additional burden of stroke and death due to abortions and full-term pregnancies would not be expected to outnumber the strokes due to OC use, the potential economic and psychological impact of this number of unintended pregnancies is substantial.[68] For the 78.5 million OC users worldwide,[2] the impact of unintended pregnancies is even greater because of much higher mortality rates with pregnancy and abortion in developing countries.[2,69] Based on estimates of unintended pregnancies, abortions, and pregnancy-related mortality,[3,69] worldwide discontinuation of OC use would almost certainly result in an increase in strokes and deaths.

In summary, while OC use is associated with increased ischemic stroke risk among current users, the absolute effect is small with current dosages. Therefore, this additional risk appears to be outweighed by the health benefits of OC use in improved birth control.

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